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Review article

Biomarkers of exposure in environment-wide association studies – Opportunities to decode the exposome using human biomonitoring data

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Abbreviations: β-HCH, β-hexachlorocyclohexane; µg/l, microgram per liter; µM/l, micromolar per liter; Σ, total; 1-HP, 1-hydroxypyrene; 2, 3-DHBA, 2,3-dihydroxybenzoic Acid; 2cx-MMHP, mono-(2-carboxymethylhexyl) phthalate; 3PBA, 3-phenoxybenzoic acid; 4F3PBA, 4-fluoro-3-phenoxybenzoic acid; 5cx-MEPP, mono-(5-carboxy-2-ethylpentyl) phthalate; 5OH-MEHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; 5oxo-MEHP, Mono-(2-ethyl-5-oxo-hexyl) phthalate; AAMA, N-acetyl-S-(2-carbamoylethyl)-L-cysteine; AAs, alkylating agents; ADI, acceptable daily intake; ALARP, as low as reasonably practicable; AM, arithmetic mean; APGAR, adaptation, partnership, growth, affection, resolve; As, arsenic; AUDIT, alcohol use disorders identification Test; BAC, blood alcohol content; BAT, biological tolerance value; BDCM, bromodichloromethane; BDE 99, 2,2′,4,4′,5-pentabromodiphenyl ether; BE, biomonitoring equivalents; BEI, biological exposure indices; BFRs, brominated flame retardants; BMD-L, benchmark dose lower confidence limit; BoE, biomarker of exposure; BPA, bisphenol A; BPA-glu, glucuronidated metabolite of BPA; BPAD, biological pathway altering dose; BPF, bisphenol F; BPS, bisphenol S; BPP, butylbenzyl phthalate; Br_2CA, 2,2-dibromovinyl-2,2-dimethylcyclopropanecarboxylic acid; BzBP, benzylbutyl phthalate; CAL REL, California acute reference exposure levels; CC, critical concentration; Cd, cadmium; cis-Cl_2CA, cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; cis-DCCA, 2,2-dichloro-2-dimethylvinyl-cyclopropane carboxylic acid; CYP, cytochrome P450; CYP1A1, cytochrome P450 1A1; CIT, citrinin; CPK, creatine phosphokinase; Cr, chromium; CRP, C-reactive protein; crea., creatinine; Cu, copper; dBA, decibel; DAP, dialkylphosphate; DBCA, 2,2-Dibromo-2-Dimethylvinyl-Cyclo-Propane Carboxylic Acid; DBCM, dibromochloromethane; DBP, di-n-butyl phthalate; DBPs, disinfection by-products; DCCA, 2,2-Dichloro-2-Dimethylvinyl-Cyclopropane Carboxylic Acid; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DEDTP, diethyl dithiophosphate; DEHP, di-2(ethylhexyl) phthalate; DEHT, di(2-ethylhexyl) terephthalate; DEP, diethyl phthalate; DETP, diethyl thiophosphate; DiBP, di-iso-butyl phthalate; DINCH, diisononyl 1,2-cyclohexanedicarboxylic acid; DiNP, diisononyl phthalate; DMP, dimethyl phosphate; DMDTP, dimethyl dithiophosphate; DMTP, dimethyl thiophosphate; DNA, deoxyribonucleic acid; DnBP, Di-n-butyl Phthalate; DON, deoxynivalenol; ECO, expired carbon-monoxide; EMF, electromagnetic field; EU's FP7, European Union's 7th Framework Programme; EWAS, environment-wide association studies; FAO, food and agriculture organization; FAS, family affluence scale; Fe, iron; FFQ, food frequency questionnaires; GAMA, N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine; GGT, γ-glutamyl transferase; GM, geometric mean; GPAQ, global physical activity questionnaires; GWAS, genetic-wide association studies; h, hours; HBCDD, hexabromocyclododecane; HBM, human biomonitoring; HCB, hexachlorbenzene; HEALS, health and environment-wide associations based on large population surveys; Hg, mercury; ICC, intraclass correlation coefficient; IL-6, interleukin-6; IMD, index of multiple deprivation; IPAQ, international physical activity questionnaires; JEM, job-exposure-matrix; LDH, lactate dehydrogenase; LOAEL, lowest observed adverse effect level; m7Gua, 7-methylguanine; MAA, 2-methoxy acetic acid; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MCT, measure of central tendency; MEHP, mono-(2-ethylhexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, mono-ethyl phthalate; MHA, methylhippuric acid; MiNP, mono-isononyl phthalate; Mn, manganese; mg/kg/day, milligram per kilogram per day; mg/m^3, milligram per cubic meter; MnBP, mono-n-butyl phthalate; MOA, mode of action; MRL, minimal risk level; MVOC, microbial volatile organic compounds; n, sample size; NDMA, N-nitrosodimethylamine; NMTCA, N-nitroso-2-methylthiazolidine-4-carboxylic acid; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; No., number; NOAEL, no observed adverse effect level; NOC, N-nitroso compounds; NOx, nitrogen oxides; NPRO, N-nitrosoproline; NPs, nanoparticles; NSAR, N-nitrososarcosine; NTCA, N-nitrosothiazolidine-4-carboxylic acid; O_3, Ozone; OH-MiNP, 7OH-mono-methyloctyl phthalate; OCPs, organochlorine pesticides; OPPs, organophosphate pesticides; OTA, ochratoxin A; oxo-MiNP, 7oxo-mono-methyloctyl phthalate; P_{90}, 90th percentile; P_{95}, 95th percentile; PAH, polycyclic aromatic hydrocarbon; Pb, lead; PBB, polybrominated biphenyls; PBBK, physiology-based biokinetic; PBDE, polybromodiphenyl ether; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDF, polychlorinated dibenzofurans; PCP, pentachlorphenol; PER, perchlorethylene; PFC, perfluorinated compounds; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; pg/ml, pictogram per milliliter; PGA, phenylglyoxylic acid; PK, pharmacokinetic; PM, particulate matter; POD, point of departure; POPs, persistent organic pollutants; PSS, perceived stress scale; PTWI, provisional tolerable weekly intake; PYR, pyrene; RfC, reference concentration; RfD, reference dose; RI, reference interval for clinical guidance; Rn, radon; RV_{95}, reference value; S-PMA, S-phenyl mercapturic acid; SC, stachybotrys chartarum; SD, standard deviation; Se, selenium; SED, systemic exposure dose; SES, socioeconomic status; SG, satratoxin G; SHS, second-hand smoke; STA, state-trait anxiety inventory; TBBPA, Tetrabromobisphenol A; TCAA, trichloroacetic acid; TCEQ ReV, reference value of the Texas commission on environmental quality; TCDD, tetrachlorodibenzo-p-dioxin; TDI, tolerable daily intake; THMs, trihalomethanes; THS, third-hand smoke; TLV, threshold limit values; trans-Cl2CA, trans-2-dichlorovinyl-2,2-dimethylcyclopropane-1-carboxylic acid; trans-DCCA, 2,2-dichloro-2-dimethylvinyl-cyclopropane carboxylic acid; U/L, units per litre; UFPs, ultrafines particles; UK, United Kingdom; US, United States; UVR, ultraviolet radiation; Zn, Zinc

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ABSTRACT

Background: The European Union's 7th Framework Programme (EU's FP7) project HEALS – Health and Environment-wide Associations based on Large Population Surveys – aims a refinement of the methodology to elucidate the human exposome. Human biomonitoring (HBM) provides a valuable tool for understanding the magnitude of human exposure from all pathways and sources. However, availability of specific biomarkers of exposure (BoE) is limited.

Objectives: The objective was to summarize the availability of BoEs for a broad range of environmental stressors and exposure determinants and corresponding reference and exposure limit values and biomonitoring equivalents useful for unraveling the exposome using the framework of environment-wide association studies (EWAS).

Methods: In a face-to-face group discussion, scope, content, and structure of the HEALS deliverable "Guidelines for appropriate BoE selection for EWAS studies" were determined. An expert-driven, distributed, narrative review process involving around 30 individuals of the HEALS consortium made it possible to include extensive information targeted towards the specific characteristics of various environmental stressors and exposure determinants. From the resulting 265 page report, targeted information about BoE, corresponding reference values (e.g., 95th percentile or measures of central tendency), exposure limit values (e.g., the German HBM I and II values) and biomonitoring equivalents (BEs) were summarized and updated.

Results: 64 individual biological, chemical, physical, psychological and social environmental stressors or exposure determinants were included to fulfil the requirements of EWAS. The list of available BoEs is extensive with a number of 135; however, 12 of the stressors and exposure determinants considered do not leave any measurable specific substance in accessible body specimens. Opportunities to estimate the internal exposure stressors not (yet) detectable in human specimens were discussed.

Conclusions: Data about internal exposures are useful to decode the exposome. The paper provides extensive information for EWAS. Information included serves as a guideline – snapshot in time without any claim to comprehensiveness – to interpret HBM data and offers opportunities to collect information about the internal exposure of stressors if no specific BoE is available.

1. Introduction

The European Union's 7th Framework Programme (EU's FP7) project HEALS – Health and Environment-wide Associations based on Large Population Surveys – started in 2013 with a term of 5 years. The objective of HEALS is the refinement of an integrated methodology and the application of analytical and computational tools for elucidating human exposome through the integrated use of advanced statistical tools for environment-wide association studies (EWAS) in support of EU-wide environment and health assessments (www.heals-eu.eu).

Important determinants for the development of diseases are genetic influences and the interaction of environmental stressors (Schwartz and Collins, 2007). Described with the complementary approach of nature and nurture, the term "environment" includes everything that is not genetic (Smith et al., 1999). Consequently, the genome needs to be complemented by the exposome (Wild, 2005, 2012). While the human "genome is fixed at conception" (but changed by mutagenic influences) (Rappaport, 2011), "the exposome encompasses life-course environmental exposures […], from the prenatal period onwards" (Wild, 2005). Based on the above, genome-wide association studies (GWAS) attempt to describe the influence of genetic factors for the development of diseases (Hirschhorn and Daly, 2005), while EWAS investigate the associations between a wide range of environmental factors and diseases (Patel et al., 2010). In this context, human biomonitoring (HBM) –procedures to determine substances or biological markers in human specimens (Angerer et al., 2007) – provides a valuable tool for understanding the magnitude of exposure from all pathways and sources. A biomarker of exposure (BoE) "may be the identification of an exogenous substance within the system, the interactive product between a xenobiotic compound and endogenous components, or other event in the biological system related to the exposure"(NRC, 1987). BoEs include either stressors themselves (e.g. the parent compounds), or their metabolites (reaction products), identified in a variety of human specimens such as blood, urine, deciduous teeth or hair (CDC, 2005).

HEALS encompasses a more integrative approach for associating environmental exposures and disease mechanisms and outcomes. Data from the external environment, e.g., measurements of chemicals in different media (e.g. air, water, soil and food), are combined with data regarding internal exposure, e.g., measurements of chemicals in urine or blood, to build the exposome and to derive environment-wide associations between exposure and disease. Starting from HBM samples, quantification of exposure biomarkers, together with identification of markers of effect and susceptibility (mainly-omics), builds the analytical exposure biology framework for unraveling the human exposome using multi-omics technologies according to the HEALS paradigm.

To evaluate HBM data, reference and exposure limit values as well as biomonitoring equivalents are useful and receive particular attention in the HEALS project. Reference values describe the upper level of the populations' background concentration (Angerer et al., 2007; Schulz et al., 2011). The HBM Commission of the German Environment Agency defines the reference value RV_{95} as "the 95 population percentile […] rounded off within the 95% confidence interval" of the respective parameter in the matrix obtained from the reference population (Schulz et al., 2011). Reference values contain no information about health-related biological exposure limits (Angerer et al., 2007).

Popular health-related biological exposure limit values are the German HBM I and II values. There is no health risk assumable if the concentration of a substance in urine or blood is below the HBM I level.